



PCSK9 and ANGPTL3 Inhibitors in Homozygous Familial Hypercholesterolemia: A Meta-analysis of Randomized Clinical Trials

Ibadete Bytyçi^{1,2} · Michael Y. Henein^{3,4} · Sefer Bytyqi⁵ · Mentor Shatri² · Drilon Gashi³ · Endrit Dragusha² · Rozafa Koliqi⁶ · Shpend Elezi^{1,2} · Adrian V. Hernandez^{7,8} · Maciej Banach^{9,10,11,12} 

Received: 7 September 2025 / Accepted: 30 November 2025 / Published online: 7 January 2026
© The Author(s), under exclusive licence to Springer Nature Switzerland AG 2026

Abstract

Objective The aim of this meta-analysis was to compare the efficacy of PCSK9 and ANGPTL3 inhibitors in patients with homozygous familial hypercholesterolemia (HoFH).

Methods We systematically searched selected electronic databases until 30 November 2024. Main end point was the effect of lipid lowering therapy on lipid profile: total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) and lipoproteins levels. The secondary end point was adverse clinical effects.

Results A total of 12 trials involving 392 patients with HoFH, were finally included in the meta-analysis. At a median follow-up of 12 months, ANGPTL3 inhibitors achieved greater reductions in TC (−49.9% versus −21.2%; p for subgroup < 0.001), LDL-C (−50.77% versus −17.88%; p for subgroup < 0.001) and TG (−48.9% versus −8.2%; p for subgroup < 0.001) compared with PCSK9 inhibitors, but had a smaller impact on HDL-C (−28.9% versus +5.2%; p for subgroup = 0.001). Apolipoprotein B decreased more with ANGPTL3i (−26.9% versus −13.2%; p for subgroup < 0.001), while lipoprotein(a) reductions were similar between groups, and apolipoprotein A remained unaffected with PCSK9i but slightly decreased with ANGPTL3i. In meta-regression, ANGPTL3i produced a greater LDL-C reduction in the negative LDL receptor (LDLR) genotype (−34.5%; p = 0.04) and showed a trend toward significance in the defective genotype (−23.1%; p = 0.07), with no significant difference in the heterozygous type. The rates of adverse events and discontinuations were not significantly different between the groups.

Conclusions PCSK9 inhibitors have lower efficacy in reducing lipid levels in HoFH compared with ANGPTL3 inhibitors, with the greatest difference seen in patients with the negative LDLR genotype. Further studies are needed to clarify efficacy across LDLR functional variants.

✉ Maciej Banach
maciej.banach@kul.pl

¹ Medical Faculty, University of Prishtina, Prishtina, Kosovo

² Clinic of Cardiology, University Clinical Centre of Kosovo, Prishtina, Kosovo

³ Imperial College of London, London, UK

⁴ University of Siena, Siena, Italy

⁵ Riinvest University, Prishtina, Kosovo

⁶ Department of Clinical Pharmacy and Biopharmacy, Pharmacy Division, Faculty of Medicine, University of Prishtina, Prishtina, Kosovo

⁷ Health Outcomes, Policy, and Evidence Synthesis (HOPES) group, Department of Pharmacy Practice, University of Connecticut School of Pharmacy, Storrs, CT 06269, USA

⁸ Unidad de Revisiones Sistemáticas y Meta-análisis (URSIGET), Vicerrectorado de Investigación, Universidad San Ignacio de Loyola (USIL), Lima 15024, Peru

⁹ Faculty of Medicine, The John Paul II Catholic University of Lublin, Lublin, Poland

¹⁰ Department of Preventive Cardiology and Lipidology, Medical University of Lodz, Łódź, Poland

¹¹ Ciccarone Center for the Prevention of Cardiovascular Disease, Johns Hopkins University School of Medicine, Baltimore, MD, USA

¹² Department of Cardiology and Adult Congenital Heart Diseases, Polish Mother's Memorial Hospital Research Institute, Łódź, Poland

Graphical Abstract

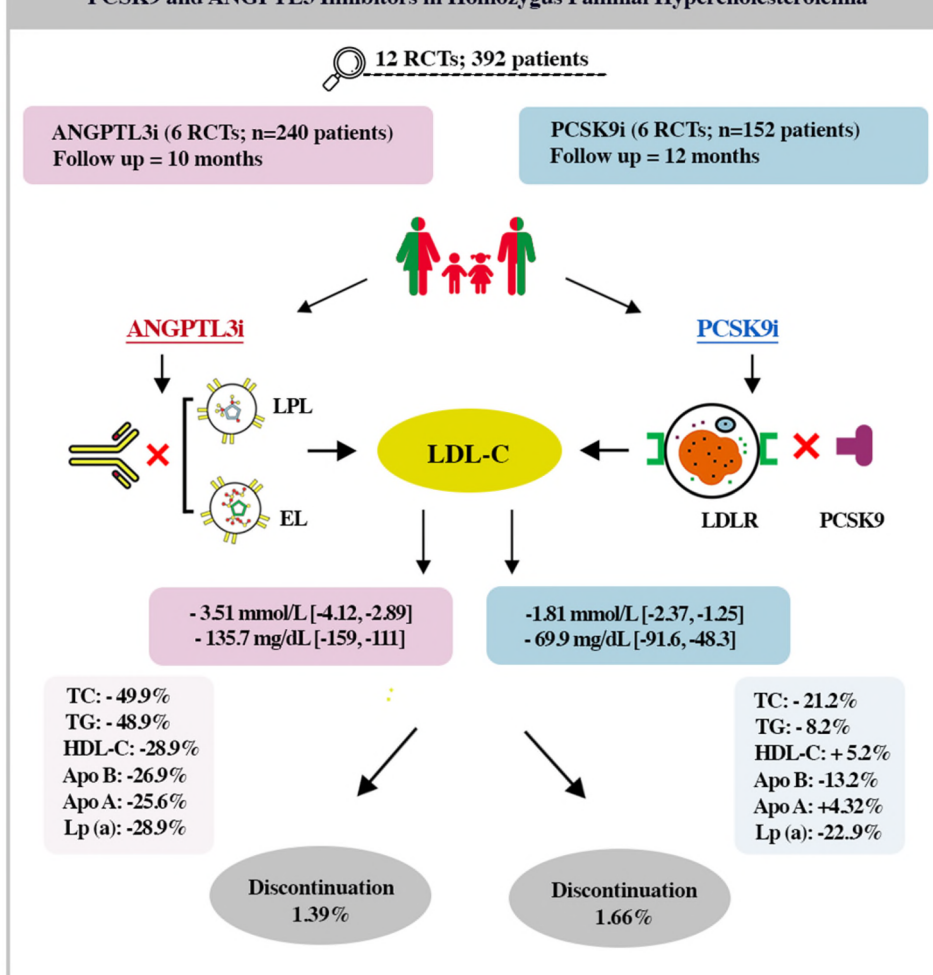
Drugs

 PEER-REVIEWED
FEATURE

PCSK9 and ANGPTL3 inhibitors in homozygous familial hypercholesterolemia: A meta-analysis of randomized clinical trials

Ibadete Bytyçi, Michael Y. Henein, Sefer Bytyqi, Mentor Shatri, Drilon Gashi, Endrit Dragusha, Rozafa Koliqi, Shpend Elezi, Adrian V. Hernandez, Maciej Banach

PCSK9 and ANGPTL3 Inhibitors in Homozygous Familial Hypercholesterolemia



ANGPTL3i angiopoietin-like protein 3 inhibitors, Apo A apolipoprotein A, Apo B apolipoprotein B, EL endothelial lipase, HDL-C high density lipoprotein cholesterol, Lp(a) lipoprotein (a), LDL-C low density lipoprotein cholesterol, LDLR LDL receptor, LPL lipoprotein lipase, PCSK9i proprotein convertase subtilisin/kexin 9 inhibitors, RCTs randomized controlled trials, TC total cholesterol, TG triglycerides.



This graphical abstract represents the opinions of the authors. For a full list of declarations, including funding and author disclosure statements, and copyright information, please see the full text online.

Key Points

In patients with homozygous familial hypercholesterolemia (HoFH), ANGPTL3 inhibitors reduced low density lipoprotein cholesterol and triglyceride levels more effectively than PCSK9 inhibitors.

The largest benefits from ANGPTL3 inhibitors were seen in patients with null (negative) LDL receptor genotypes, suggesting genotype-based differences in treatment response.

Both drug classes had similar safety profiles, with no major differences in adverse events or discontinuations.

1 Introduction

Homozygous familial hypercholesterolemia (HoFH) is an autosomal semidominant disease characterized by markedly high levels of low-density lipoprotein cholesterol (LDL-C) leading to an increased risk for premature atherosclerotic cardiovascular disease (ASCVD), high burden of cardiovascular (CV) outcomes and early mortality [1, 2]. It is caused by pathogenic variants in the LDL receptor (LDLR) gene or other genes affecting LDLR function [3]. HoFH affects approximately 1 in 160,000 to 360,000 individuals worldwide [4, 5]. Despite its significant health implications, underdiagnosis and undertreatment remain major challenges in managing this condition. Current estimates suggest that approximately 30,000 people globally have HoFH; however, less than 5% of these are properly identified and treated [4, 5]. Genetic alterations in HoFH that result in minimal or absent LDL receptor (LDLR) expression (null homozygotes) lead to significantly higher LDL-C levels compared with alterations that only partially reduce LDLR expression, such as having two non-null alleles or one null and one non-null allele (non-null homozygotes) [6]. This distinction is crucial, as HoFH accelerates the onset of ASCVD, with individuals carrying null-null LDLR variants at a higher risk of premature ASCVD. Untreated patients with HoFH typically do not survive beyond the third decade, underscoring the importance of early intervention to optimally manage LDL-C and to lower the risk of CV events [7, 8].

The combination of lipid-lowering therapy (LLT), which includes various available therapies and lipoprotein apheresis (LA), is the cornerstone of managing homozygous familial hypercholesterolemia (HoFH), alongside lifestyle modifications [1]. Guidelines recommend early initiation of multiple LLTs such as high-intensity statins, ezetimibe,

PCSK9 inhibitors (evolocumab or alirocumab), angiopoietin-like 3 (ANGPTL3) inhibitors such as evinacumab and mipomersen and lomitapide [1, 7, 9–11]. Statins and PCSK9 inhibitors, which upregulate hepatic LDL receptors, reduce LDL-C by ~30% but are less effective in severe HoFH with two null LDLR alleles [1, 12, 13]. Lomitapide, acting independently of LDLR, is an alternative but carries some safety concerns including gastrointestinal issues and hepatic steatosis [14, 15]. Angiopoietin-like 3 (ANGPTL3) is a key regulator of lipid metabolism, primarily inhibiting lipoprotein lipase (LPL) and endothelial lipase (EL). Evinacumab, an ANGPTL3 monoclonal antibody, has proved effective in patients aged ≥ 12 years, in reducing LDL-C by ~50% in the ELIPSE HoFH trial when used alongside maximally tolerated LLTs and/or lipoprotein apheresis [16, 17]. The purpose of this meta-analysis was to evaluate and compare the efficacy and safety of innovative LLT-PCSK9 and ANGPTL3 inhibitors in the treatment of HoFH.

2 Methods

2.1 Search Strategy and Selection Criteria

We conducted the study in accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18]. As this is a meta-analysis, there was no need for Institutional Review Board (IRB) approval or patient informed consent. To define the clinical question and formulate a comprehensive search strategy, we applied the PICOS model, focusing on population, intervention, comparison, outcomes and study design [19] (Supplementary Table S1).

Databases were systematically searched up to 30 November 2024. These included PubMed-Medline, EMBASE, Scopus, Google Scholar, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov, using specific keywords to identify relevant studies: ‘Proprotein convertase subtilisin/kexin type 9’ OR ‘PCSK9 inhibitors’ OR ‘PCSK9i’ OR ‘Angiopoietin-like protein 3 inhibitors’ OR ‘ANGPTL3 inhibitors’ OR ‘ANGPTL3 i’ OR ‘Alirocumab’ OR ‘Evolocumab’ OR ‘Evinacumab’ AND ‘Homozygous Familial Hypercholesterolemia’ OR ‘Homozygous FH’ OR ‘HoFH’ (Supplementary Table S2). To identify additional relevant studies, references from review articles and abstracts from key congresses, such as the European Society of Cardiology (ESC), European Atherosclerosis Society (EAS), American Heart Association (AHA) and American College of Cardiology (ACC) were reviewed. The wildcard term ‘*’ was employed to enhance search sensitivity, with the search restricted to human studies published in English and no filters applied. Each article was independently evaluated by two reviewers (M.S. and D.G.). In cases of uncertainty

regarding the suitability of a paper, the senior investigators (I.B. and M.B.) were consulted. The selected articles were assessed in full text, and data extraction was performed by the same researchers, while data analysis was conducted by two other researchers (S.B. and I.B.). Typically, the extracted data were compared with the original articles, and errors were corrected as needed. For each trial, the risk of bias was independently assessed by the same investigators using the revised Cochrane risk-of-bias tool for randomized trials (Cochrane RoB2 tool), which evaluates five domains: the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and the selection of reported results. The risk of bias in each study was categorized as ‘low,’ ‘high’ or ‘unclear’ [20].

Articles were considered eligible if they reported the treatment of patients with HoFH with PCSK9 inhibitors (PCSK9i) or ANGPTL3 inhibitors (ANGPTL3i) under the following criteria: (i) trials investigating the efficacy and/or safety of PCSK9i/ANGPTL3i pre-post-treatment in patients with HoFH after treatment with standard lipid-lowering therapy (LLT); (ii) studies using genetic and/or clinical criteria for the diagnosis of HoFH according to the available guidelines; and (iii) trials with a follow-up period of at least 3 months. Exclusion criteria were: (i) insufficient statistical data to test the efficacy and safety of treatment, (ii) patients with heterozygous FH, (iii) studies not in humans, and (iv) ongoing studies (unless they had reported relevant interim results). Studies of unapproved therapies in patients with homozygous familial hypercholesterolemia (HoFH) were excluded from the meta-analysis.

2.2 Outcome Variables

The primary end point was to assess the efficacy and safety of PCSK9 inhibitors and ANGPTL3 inhibitors in patients with HoFH. Efficacy parameters for PCSK9i (alirocumab, evolocumab) and ANGPTL3i (evinacumab) included changes in lipid profiles, such as total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and lipoprotein levels, including lipoprotein(a) (Lp(a)), apolipoprotein A (Apo-A) and apolipoprotein B (Apo-B).

The secondary end point was related to safety, with parameters including the prevalence of adverse events (AEs) and inverse variance used for subgroup analyses between groups.

2.3 Data Synthesis and Statistical Analyses

The meta-analysis was conducted using R Statistical Software (v3.5.1, Boston, MA, USA) with the ‘meta’ and ‘metafor’ packages. For each randomized controlled trial (RCT), treatment effects were expressed as mean differences (MD)

with 95% confidence intervals (CIs). Separate meta-analyses were conducted for PCSK9 inhibitors and ANGPTL3 inhibitors in patients with HoFH [21].

Heterogeneity was assessed with the Cochran’s Q -test and quantified using the I^2 statistic, and τ^2 was estimated using the restricted maximum-likelihood (REML) method [22]. Subgroup analysis of summary of lipid profile and lipoproteins were compared between two group of treatments using a random effect model with Hartung–Knapp adjustment and differences between subgroups were tested using the χ^2 test for subgroup differences.

Meta-regression analyses evaluated the effect of continuous covariates (age) and categorical variables (genotype: negative, defective and heterozygous) on percentage LDL-C reduction. The prevalence of adverse events (AEs) was analysed as pooled proportions with 95% CIs using a random-effects model (DerSimonian–Laird), with data transformed using the Freeman–Tukey double arcsine method where appropriate. Forest plots were generated without p value columns, with customized shapes, sizes and CI whiskers, as specified in the code. All statistical tests were two-tailed, and p values < 0.05 were considered statistically significant. Publication bias was assessed through visual inspection of funnel plots and Egger’s test.

3 Results

3.1 Characteristics of Included Trials

An initial search yielded 4687 articles, which were screened for relevance, leading to the selection of 348 articles. Following a rigorous selection process, 12 trials involving 392 patients with HoFH were included in the meta-analysis [23–34] (Supplementary Fig. S1). Six RCTs utilized PCSK9i ($n = 152$ patients), while the remaining six RCTs applied treatment with ANGPTL3i ($n = 240$ patients). The characteristics of included trials is presented in Table 1. The mean age of the patients was 31.7 ± 13 and 48.4% were females. A total of 55.2% of patients were with cardiovascular disease (CVD) at the trials’ inclusion. The prevalence of White patients was significantly higher compared with the Black, Asian or other races (75.4, 2.4, 8.5, 11%, $p < 0.01$; respectively).

When comparing the pooled mean differences (MDs) of patients treated with LLTs, patients age in the groups of PCSK9i and ANGPTL3i trials was similar (30.8 ± 14.8 versus 33.3 ± 12.2 , $p = 0.07$). However, the prevalence of female patients and the presence of CVD were significantly lower in patients treated with PCSK9i compared with those treated with ANGPTL3i ($p < 0.01$ for both), (Supplementary Table S3). The distribution of LDLR mutation types did not differ between the two treatment groups for the negative

Table 1 Main characteristics of studies included in the present meta-analysis

First author (trial year)	Study design	Location	Population	Sample size	Primary end points	Other end points	Follow-up (months)
Stein (TESLA, Part A) 2013 [23]	RCT (single blind) NCT01588496	USA, Europe, Africa	HoFH (genetic or clinical criteria)	8	Lipid profile Lipoproteins	Adverse events	6
Raal (TESLA, Part B) 2015 [24]	RCT (double blind) NCT01588496	USA, Europe, Middle East, Africa 17 centers	HoFH (genetic or clinical criteria)	33	Lipid profile Lipoproteins	Adverse events	3
Blom (ODYSSEY HoFH) 2020 [25]	RCT (double blind) NCT03156621	USA 27 centers	HoFH (genetic criteria)	45	Lipid profile Lipoproteins Hospitalization	Adverse events	3
Santos (TAUS-SIG) 2020 [26]	RCT (double blind) NCT01624142	USA 44 centers	HoFH (genetic criteria)	106	Lipid profile Lipoproteins Hospitalization	Adverse events	60
Bruckert 2022 [27]	RCT (open label) NCT03510715	10 countries, Brazil, Canada, Netherland etc.	HoFH (genetic criteria)	18	Lipid profile Lipoproteins	Adverse events	12
Bansal (RAMAN) 2021 [28]	RCT (open label) NCT03403374	India	HoFH (genetic or clinical criteria)	30	Lipid profile Lipoproteins	Adverse events	12
Banerjee 2019 [29]	RCT (double blind) NCT02265952	USA, Canada, Netherland 5 centers	HoFH (genetic criteria)	9	Lipid profile	NR	3
Raal (ELIPSE HoFH) 2023 (a) [30]	RCT (double blind) NCT03399786	11 countries 30 centres	HoFH (genetic or clinical criteria)	44	Lipid profile Lipoproteins	Adverse events	6
Raal (ELIPSE HoFH) 2023 (b) [30]	RCT (double blind) NCT03399786	11 countries 30 centres	HoFH (genetic or clinical criteria)	20	Lipid profile Lipoproteins	Adverse events	12
Stefanutti 2024 [31]	RCT (open label)	Italy	HoFH (genetic criteria)	7	Lipid profile Lipoproteins	Adverse events	6
Gaudet 2024 [32]	RCT (double blind) NCT03409744	USA, Australia, Canada etc. 38 centers	HoFH (genetic or clinical criteria)	46	Lipid profile Lipoproteins	Adverse events	26
Béliard (OLE ELIPSE HoFH) 2024 [33]	RCT (open label) 2024/A01549-38	France	HoFH (genetic criteria)	12	Lipid profile Lipoproteins	Adverse events	10
Wiegman (PART B) 2024 [34]	RCT (open label) NCT04233918	USA, Austria, Ukraine etc. 10 centers	HoFH (genetic or clinical criteria)	14	Lipid profile Lipoproteins	Adverse events	6

All patients were on LLT (statin and ezetimibe). Apheresis was used in 77% of studies, except for Banerjee 2019, Stein 2013, and Raal 2015. *HoFH* homozygous familial hypercholesterolemia, *NR* non-reported, *RCT* randomized clinical trial

and defective categories (41.5% versus 37.5%; 37.7% versus 38.2%, respectively; $p > 0.05$ for both). However, the heterozygous type was more prevalent in the ANGPTL3i group (21.3% versus 9.8%; $p = 0.031$), whereas the other type was more common in the PCSK9i group (10.9% versus 2.9%; $p = 0.044$; Supplementary Table S4).

3.2 Comparative Efficacy of PCSK9i and ANGPTL3i on Lipid Profiles and Lipoproteins

At a median follow-up of 12 months, in the separation analysis using an inverse variance model, the ANGPTL3i group showed a significant mean reduction in TC [MD

Mean change in lipid profile in the ANGTP3i group

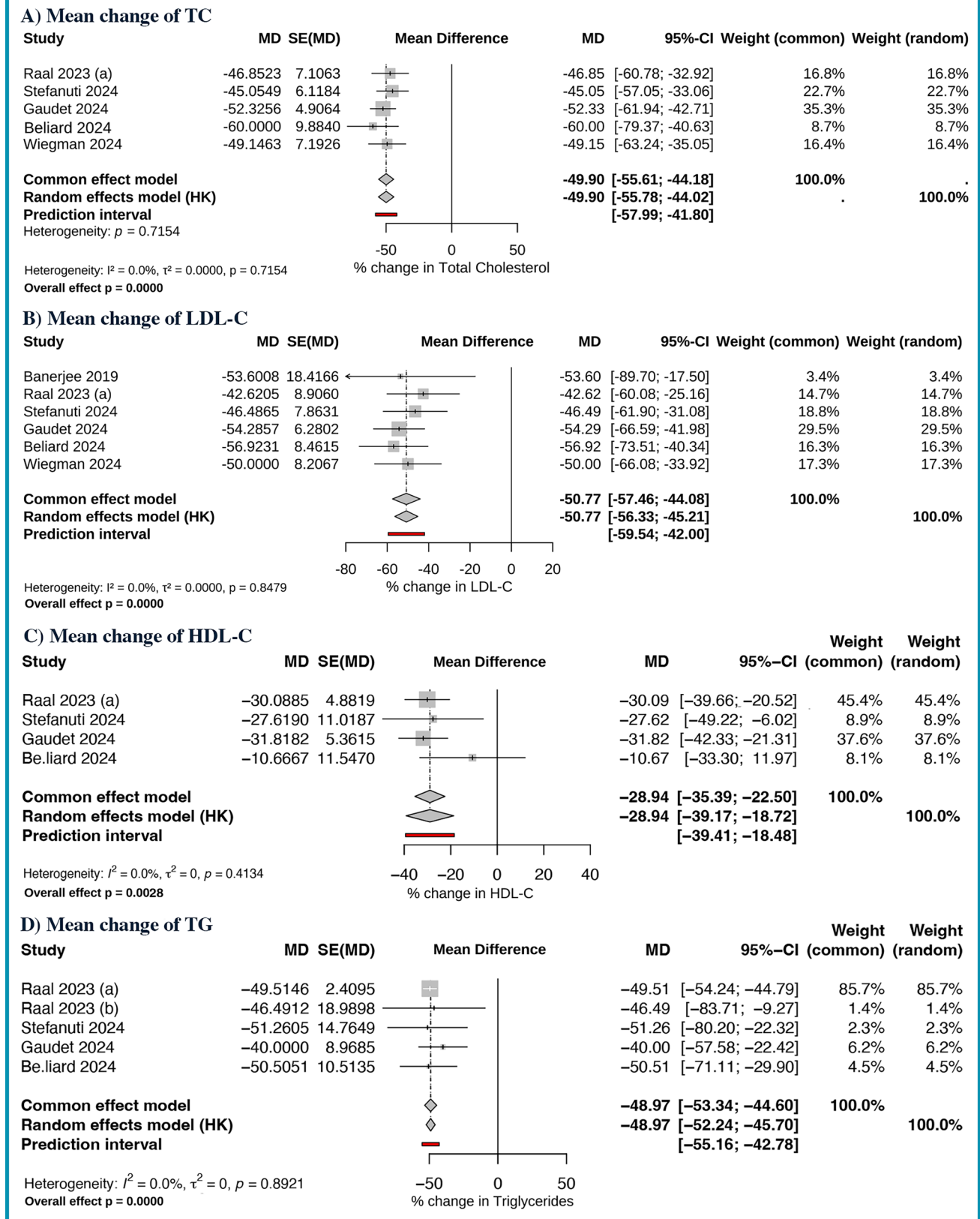


Fig. 1 Mean change in lipid profile in the ANGTP3i group. *CI* confidence interval, *HDL-C* high density lipoprotein cholesterol, *LDL-C* low density lipoprotein cholesterol, *MD* mean difference, *TC* total cholesterol, *TG* triglycerides

–49.9% (–55.7 to –44.0; $p < 0.001$), LDL-C [MD –50.77% (–56.3 to –45.2; $p < 0.001$)] and TG [MD –50.5% (–52.2 to –45.7; $p < 0.001$)], as well as a significant reduction in HDL-C [MD –28.9% (–39.1 to –18.7; $p = 0.002$); Fig. 1]. Similarly, but to a lesser extent, the PCSK9i group demonstrated mean reductions in TC [MD –21.21% (–27.7 to –15.7; $p = 0.003$)] and LDL-C [MD –17.8% (–26.0 to –9.6; $p = 0.002$)], along with a significant increase in HDL-C [MD 5.25% (1.26 to 9.15; $p = 0.021$)], while the reduction in TG was not statistically significant [MD –8.25% (–28.7 to 12.2; $p = 0.29$); Fig. 2]. Similarly, both PCSK9i and ANGPTL3i reduced Apo-B and Lp(a), whereas Apo-A remained unaffected in the PCSK9i group but showed a slight, yet statistically significant, decrease in the ANGPTL3i group ($p < 0.05$ for all; Supplementary Figs. S2 and S3).

When comparing the subgroup analyses on lipid profile and lipoproteins, the ANGPTL3i group showed a greater mean reduction in TC [MD –49.9% versus –21.2%; $p_{\text{for subgroup}} < 0.001$] and LDL-C [MD –50.7% versus –17.8%; $p_{\text{for subgroup}} < 0.001$] compared with the PCSK9i group. In contrast, HDL-C increased slightly more with PCSK9i than with ANGPTL3i [5.2% versus –28.9%; $p_{\text{for subgroup}} = 0.001$]. TG levels did not change significantly with PCSK9i, whereas they were markedly reduced with ANGPTL3i [–8.2% versus –48.9%; $p_{\text{for subgroup}} < 0.001$; Supplementary Figs. S4 & S5; Graphical Abstract]. Likewise, Apo-B decreased more with ANGPTL3i than with PCSK9i [–26.9% versus –13.2%; $p_{\text{for subgroup}} < 0.001$], whereas the reduction in Lp(a) was comparable between the two groups (–29.8% versus –22.9%; $p_{\text{for subgroup}} = 0.54$). Apo-A remained unaffected in the PCSK9i group but showed a slight decrease with ANGPTL3i (Supplementary Fig. S6). A summary of ANGPTL3 and PCSK9 inhibitors efficacy is presented in Fig. 3.

3.2.1 Effect of LDLR Genotype and Age on LDL-C Reduction

The ANGPTL3i group showed a significantly greater reduction in LDL-C among patients with the negative genotype; for every 10% increase, the mean additional reduction was –34.5% (95% CI –54.7 to –14.2; $p = 0.04$) compared with PCSK9i. A similar trend was observed in the defective genotype [–23.1% (95% CI –44.7 to 1.55); $p = 0.07$], although this did not reach statistical significance. No significant difference was observed in the heterozygous genotype [intercept = –18.9% (95% CI –52.1 to 14.3); $p = 0.36$; Supplementary Fig. S7]. Age did not have a significant mediating effect on the mean reduction of LDL-C [intercept = –0.44 (95% CI 2.5 to 1.6); $p = 0.669$; Supplementary Fig. S8].

3.2.2 Safety and Tolerability of PCSK9i and ANGPTL3i in Patients with HoFH

At the end of the follow-up period, no significant difference was observed between the groups with regards to the prevalence of AEs or treatment discontinuation ($p > 0.05$ for both). The prevalence of gastroenteritis, abdominal pain, nausea and vomiting was higher, while injection site reactions, upper respiratory tract infections and elevated creatine kinase were less prevalent in the ANGPTL3i group compared to PCSK9i ($p < 0.05$ for all). Other adverse clinical events were not significantly different between the groups (Table 2).

3.3 Risk of Bias Assessment

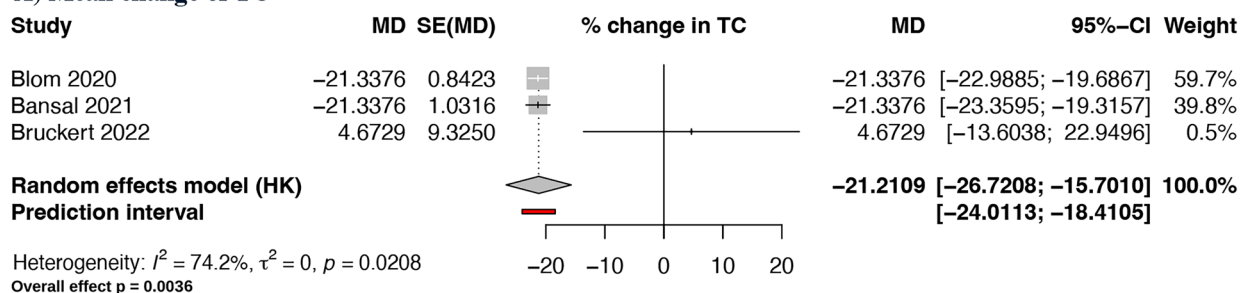
The assessment of risk of bias in the included studies using RoB2 for RCTs showed that most studies had moderate-to-high quality level in defining objectives and the main outcomes (Supplementary Table S4). Also, there was no evidence for publication bias as evaluated by the Egger's test for our findings.

4 Discussion

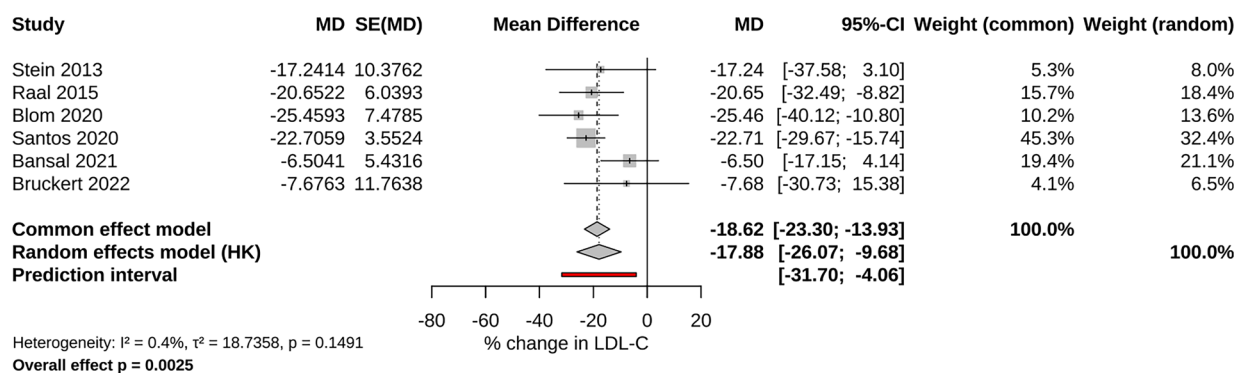
HoFH remains underdiagnosed and often identified too late, leading to suboptimal treatment despite the availability of several LLTs for reducing LDL-C [2, 35]. Also, guideline-recommended LDL-C targets are rarely achieved in these patients, largely owing to the heterogeneous nature of the condition, which results from its diverse genetic and phenotypic presentations. Consequently, achieving optimal LDL-C levels is challenging, and newer therapies are typically added to existing treatments rather than replacing them. This practice complicates accurate evaluation of the individual efficacy of new therapies, as issues of external validity and generalizability arise from the wide variety of background treatments [1, 9, 36]. In addition, CRISPR-based gene editing is a promising future therapy for HoFH, aiming for long-term LDL-C reduction via a single hepatic dose targeting PCSK9 or ANGPTL3. Early studies, including VERVE-101, have shown encouraging preliminary results, though this approach remains in early clinical development [37]. In selected cases, liver transplantation remains an option for HoFH—particularly for patients with null mutations and refractory hypercholesterolemia despite maximal therapy. Transplantation restores functional LDL receptors and markedly lowers LDL-C, but its risks limit use to specialized centres [38]. Patients with HoFH are also prone to premature aortic stenosis from lifelong extreme LDL-C exposure,

Mean change in lipid profile in the PCSK9i group

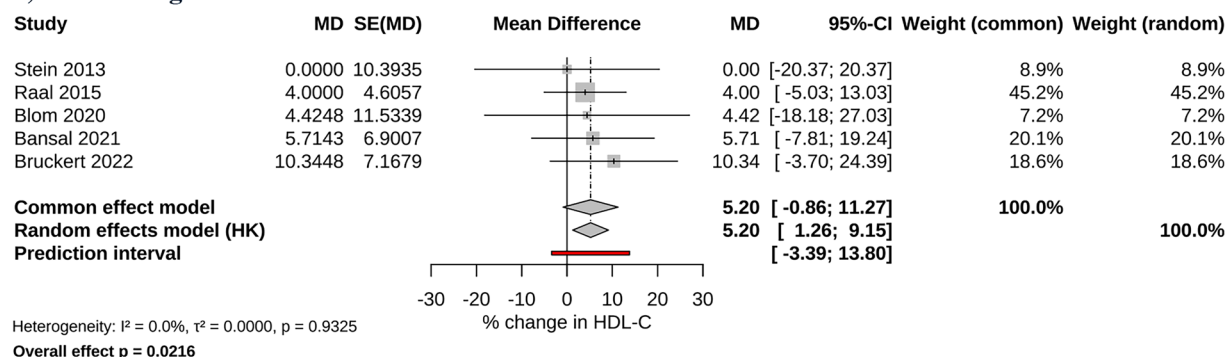
A) Mean change of TC



B) Mean change of LDL-C



C) Mean change of HDL-C



D) Mean change of TG

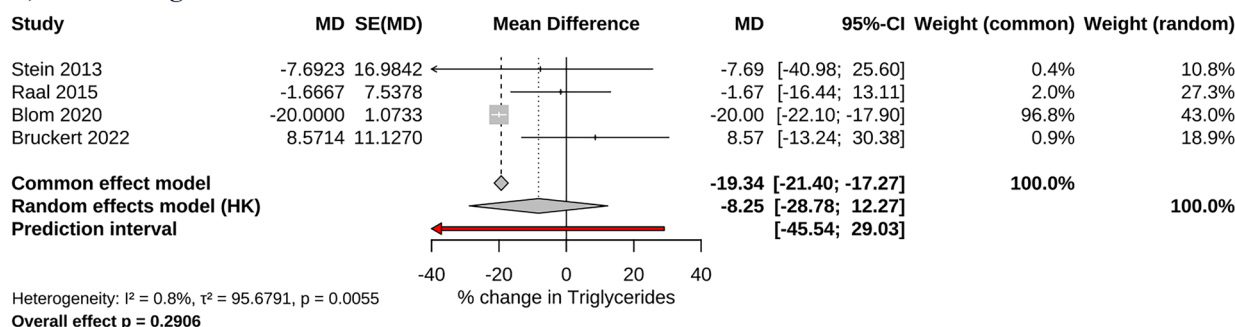


Fig. 2 Mean change in lipid profile in the PCSK9i group. *CI* confidence interval, *HDL-C* high density lipoprotein cholesterol, *LDL-C* low density lipoprotein cholesterol, *MD* mean difference, *TC* total cholesterol, *TG* triglycerides

Summary of mean changes in lipid profile and lipoproteins by group

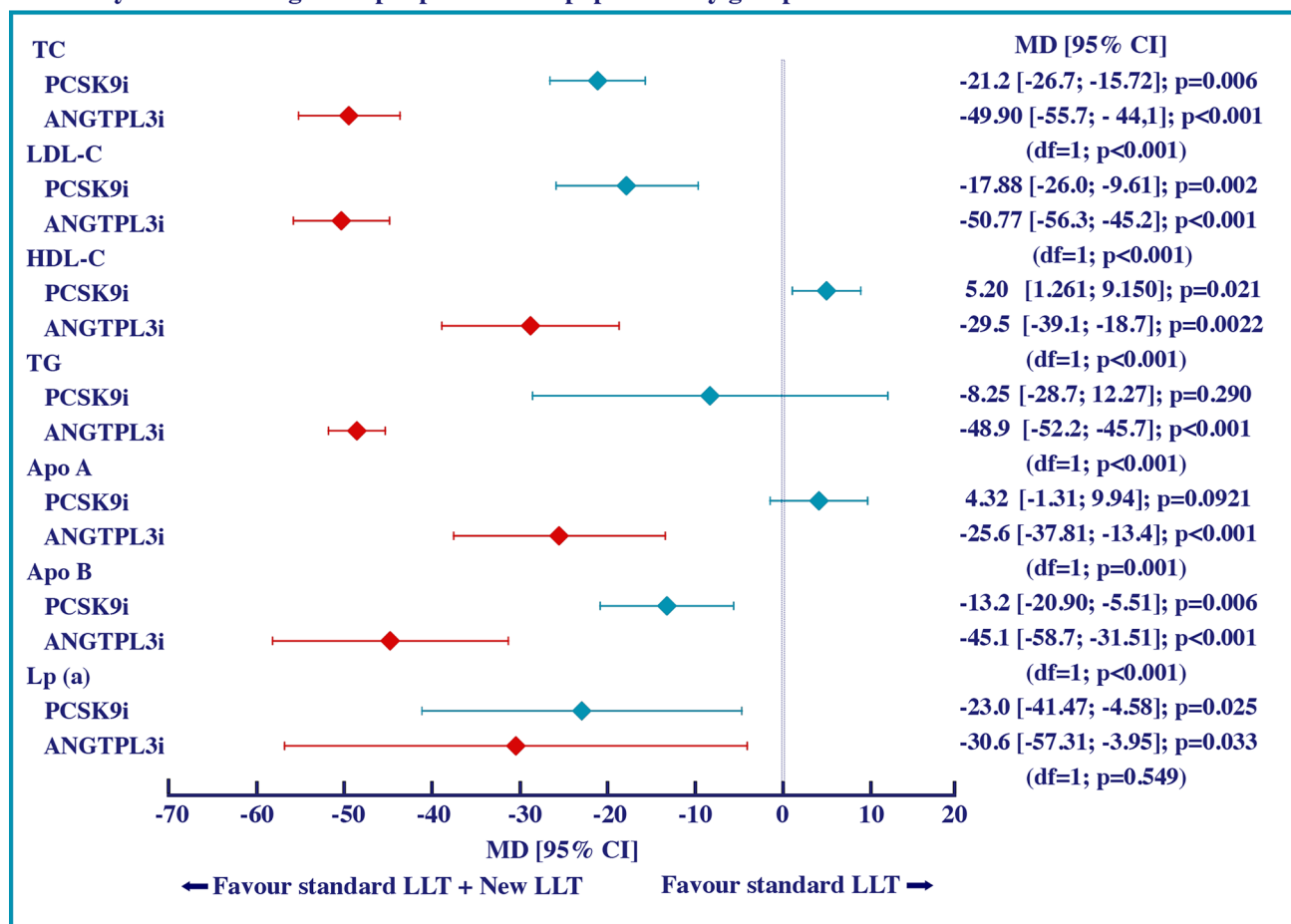


Fig. 3 Summary mean change of lipid profile. *Apo* apolipoprotein, *CI* confidence interval, *HDL-C* high density lipoprotein cholesterol, *LDL-C* low density lipoprotein cholesterol, *Lp (a)* lipoprotein (a), *MD* mean difference, *TC* total cholesterol, *TG* triglycerides

which accelerates valvular calcification; therefore, regular echocardiographic monitoring is recommended, and new therapies may effectively decrease this risk [39].

To our knowledge, this is the first meta-analysis that compares the efficacy and safety of PCSK9i and ANGPTL3i in patients with HoFH. The results of our meta-analysis, which included 12 RCTs involving 392 early adult patients with HoFH and a median follow-up of 6 months, demonstrate a greater reduction in the lipid profile (TC, LDL-C, TG) and lipoproteins such as ApoB and Lp(a) in patients treated with ANGPTL3i compared with those receiving PCSK9i. Conversely, HDL-C showed a slightly greater increase in the PCSK9i groups, while Apo A levels remained unaffected in both treatment groups.

PCSK9 monoclonal antibody therapy (evolocumab or alirocumab, at approved doses for HoFH) has shown significant efficacy in reducing LDL-C levels for many patients with HoFH [23–28, 40, 41]. However, the extent of LDL-C reduction can vary widely depending on the activity of the LDL receptor (LDLR), as well as individual genetic factors

influencing response to treatment. Pharmacogenetic profiling may help predict the effectiveness of these therapies, and in some cases, the treatment response is best assessed through a trial of different therapeutic approaches [1, 2, 36]. Based on the 2023 European Atherosclerosis Society (EAS) Consensus Statement on HoFH, if patients show > 15% additional LDL-C reduction, PCSK9-directed therapy may continue [1, 7]. This variability underscores the importance of personalized treatment strategies for achieving optimal lipid control in patients with HoFH. On the other hand, ANGPTL3 monoclonal antibody, targets angiotensin-like protein 3, which plays an important role in regulating lipid-lipoprotein metabolism. Licensed for patients with HoFH aged ≥ 12 years, evinacumab gained approval based on results from the Phase 3 ELIPSE HoFH trial [1, 29]. Importantly, response to evinacumab was not dependent on LDL receptor (LDLR) genotype, with similar outcomes in patients with biallelic null variants or those with predicted residual LDL receptor function. Despite the difference in the pharmacokinetics of these two medications groups, at the end of the follow-up

Table 2 The prevalence of adverse events among patients treated with PCSK9 and ANGPTL3 inhibitors

Adverse events	ANGPTL3i		PCSK9i	
	Prevalence (%)	95% CI	Prevalence (%)	95% CI
Serious TEAE	9.091	4.930–15.04	12.03	9.302–18.29
Gastroenteritis	4.895	1.990–9.826	1.250	0.259–3.609
Abdominal pain	4.196	1.555–8.909	0.000	0.000–1.525
Nausea	6.993	3.404–12.48	0.000	0.000–1.525
SAMS	0.000	0.000–2.547	3.750	1.729–6.999
Vomiting	3.497	1.145–7.971	0.000	0.000–1.525
Diarrhea	4.196	1.555–8.909	4.583	2.310–8.053
Constipation	0.000	0.000–2.547	0.000	0.000–1.525
Neurologic disorders	2.797	0.767–7.007	1.250	0.259–3.609
Hepatic disorders	0.000	0.000–2.547	0.000	0.000–1.525
Headache	10.08	7.080–18.35	8.333	5.164–12.57
Myalgia	3.497	1.145–7.971	3.750	1.729–6.999
Sleep disorders	0.000	0.000–2.547	0.000	0.000–1.525
Rash/Skin disorders	0.000	0.000–2.547	0.833	0.101–2.978
Influenza like disease	4.196	1.555–8.909	8.750	5.498–13.06
Upper respiratory tract infection	4.196	1.555–8.909	10.41	6.855–14.99
CK < 3, < 10 × ULN	0.000	0.000–2.547	5.833	3.225–9.594
CK > 10 × ULN	0.000	0.000–2.547	3.750	1.729–6.999
ALT > 3 × ULN	2.098	0.435–6.008	2.917	1.181–5.917
AST > 3 × ULN	2.098	0.435–6.008	2.917	1.181–5.917
Discontinuation	1.399	0.170–4.961	1.667	0.456–4.212
Injection side effects	0.000	0.000–2.547	7.500	4.505–11.59
Total (fixed effects)	2.334	1.837–2.922	2.775	2.349–3.253
Total (random effects)	2.334	1.250–3.744	2.775	1.475–4.467

ALT alanine transaminase, AST aspartate transaminase, CK creatine kinase, SAMS statin-associated muscle symptoms, TEAE treatment-emergent adverse event, ULN upper limit of normal

period, no significant differences were found between the treated groups in terms of the prevalence of treatment-emergent adverse events or treatment discontinuation.

Differences in efficacy and safety may relate to the use of apheresis (present in 77% of studies, except for Banerjee 2019, Stein 2013, and Raal 2015), study design (double-blind, open-label, or single-arm), and patient status (naive versus extension) [23, 24, 29]. However, owing to the small number of patients in some studies, these factors likely had a limited influence on overall results [23, 24, 29]. The genotypic findings from our meta-analysis suggest a plausible increased reduction in LDL receptor (LDLR) activity, given that the cohort was relatively young and presented with markedly elevated baseline LDL-C levels, potentially reflecting significant LDLR dysfunction. Meta-regression analysis showed that ANGPTL3 inhibitors achieved a significantly greater LDL-C reduction in individuals with the negative genotype (−34.5%; $p = 0.04$) and a trend toward greater reduction in those with the defective genotype (−23.1%; $p = 0.07$) compared with PCSK9 inhibitors, with no significant difference observed in the heterozygous type.

Age was not a significant mediator of LDL-C reduction ($p = 0.66$). These findings suggest that genotype may influence treatment response, while age appears to have minimal impact. Furthermore, patients with baseline LDL-C levels greater than 13 mmol/L (500 mg/dL) did not achieve consistent lipid-lowering effects with PCSK9i, in contrast to those with lower baseline LDL-C levels (< 13 mmol/L or < 500 mg/dL), thus further supporting the hypothesis of LDLR impairment. In summary, the variability in responses to ANGPTL3i and the apparent discrepancies compared to other studies may be attributable to the LDLR genotype of the patient population [27, 28, 34, 36, 42, 43].

4.1 Strength and Limitations

Our meta-analysis highlights the efficacy and safety of new lipid-lowering therapies (ANGPTL3i and PCSK9i) in patients with HoFH, one of the most challenging groups of dyslipidemic patients. Owing to suboptimal treatment, patients with HoFH carry a high risk for ASCVD,

contributing to a significant burden of CV outcomes and premature mortality.

Our meta-analysis has some obvious limitations. Moderate heterogeneity was noted in some of the analyses, although we applied a random-effects model to reduce its impact. Another limitation is that this meta-analysis was not registered in PROSPERO. Moreover, the trials included were single-arm, which precluded direct comparisons. Nonetheless, the sub-analysis, using pooled mean differences with inverse variance, refuted any impact of the variations in sample size or age on the results. The available data were insufficient to draw definitive conclusions about the effectiveness and safety of the two new drug classes, especially for genetic mutation-based subgroups, primarily because of the limited number of trials. The small number of studies in the meta-regression ($k < 10$) reduced power to detect moderator effects and increased the risk of unstable estimates, particularly for the compound-heterozygous subgroup. Future studies are needed to assess LDL-C response by genotype and to enable more precise, individualized treatment strategies for this patient population.

In conclusion, this meta-analysis demonstrated that PCSK9 inhibitors are less effective in reducing LDL-C levels in patients with HoFH compared with ANGPTL3 inhibitors, especially in those with a negative LDLR genotype. Further studies are needed to compare the effectiveness of both treatments across different functional variations of LDL receptors in patients with HoFH.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s40265-025-02272-z>.

Acknowledgments This meta-analysis was prepared on behalf of the International Lipid Expert Panel (ILEP). The results of this meta-analysis were presented during the oral session at the European Society of Cardiology (ESC) Congress 2025 in Madrid: Session: Cardiovascular Disease in Primary Care, 30 August 2025. Preprint available online from 7 February 2025: Ibadete Bytyci, Michael Henein, Sefer Bytyqi, et al. PCSK9 and ANGPTL3 inhibitors in homozygous familial hypercholesterolemia: A meta-analysis of randomized clinical trials. Authorea. February 07, 2025. <https://doi.org/10.22541/au.173893158.83178932/v1>

Funding No external funding was used in the preparation of this manuscript.

Declarations

Conflict of interest Speaker's bureau: MB: Amgen, Adamed, Daiichi Sankyo, KRKA, MSD, Polpharma, Mylan/Viatris, Novartis, Novo-Nordisk, Pfizer, Sanofi, Teva, Zentiva; consultant to Adamed, Amgen, Daiichi Sankyo, Lilly, MSD, New Amsterdam, Novartis, Novo-Nordisk, Sanofi, Teva; Grants from Amgen, Daiichi Sankyo, Viatris, Sanofi, and Teva. All other authors have no conflict of interest.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Data availability statement All data generated or analysed during this study are included in this published article (and its supplementary information files).

Code availability Not applicable.

Author contributions I.B. and S.E.: conceptualization, study design, methodology and project administration; I.B., S.B., D.G., M.S., E.D.: data analysis and writing the first draft of manuscript. M.B., M.Y.H., I.B., R.K., A.V.H., S.E.: review manuscript. I.B., M.B., A.V.H. revised the manuscript and prepared the final version. All authors have read and agreed to the final version of the manuscript.

References

1. Cuchel M, Raal FJ, Hegele RA, Al-Rasadi K, Arca M, Averna M, et al. 2023 Update on European Atherosclerosis Society Consensus Statement on Homozygous Familial Hypercholesterolaemia: new treatments and clinical guidance. *Eur Heart J*. 2023;44:2277–91.
2. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *Eur Heart J*. 2013;34:3478–90.
3. Vrablik M, Tichý L, Freiburger T, Blaha V, Satny M, Hubacek JA. Genetics of familial hypercholesterolemia: new insights. *Front Genet*. 2020;11:574474.
4. Beheshti SO, Madsen CM, Varbo A, Nordestgaard BG. Worldwide prevalence of familial hypercholesterolemia: meta-analyses of 11 million subjects. *J Am Coll Cardiol*. 2020;75:2553–66.
5. Tromp TR, Hartgers ML, Hovingh GK, Vallejo-Vaz AJ, Ray KK, Soran H, et al. Worldwide experience of homozygous familial hypercholesterolaemia: retrospective cohort study. *Lancet*. 2022;399:719–28.
6. Bruckert E. Recommendations for the management of patients with homozygous familial hypercholesterolaemia: overview of a new European Atherosclerosis Society Consensus Statement. *Atheroscler Suppl*. 2014;15:26–32.
7. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139:e1082–143.
8. Bélanger AM, Akioyamen L, Alothman L, Genest J. Evidence for improved survival with treatment of homozygous familial hypercholesterolemia. *Curr Opin Lipidol*. 2020;31:176–81.
9. France M, Rees A, Datta D, Thompson G, Capps N, Ferns G, et al. HEART UK statement on the management of homozygous familial hypercholesterolaemia in the United Kingdom. *Atherosclerosis*. 2016;255:128–39.
10. Brunham LR, Ruel I, Aljenedil S, Riviere JB, Baass A, Tu JV, et al. Canadian Cardiovascular Society position statement on familial hypercholesterolemia: update 2018. *Can J Cardiol*. 2018;34:1553–63.
11. Raal FJ, Hovingh GK, Catapano AL. Familial hypercholesterolemia treatments: guidelines and new therapies. *Atherosclerosis*. 2018;277:483–92.

12. Moriarty PM, Parhofer KG, Babirak SP, et al. Alirocumab in patients with heterozygous familial hypercholesterolaemia undergoing lipoprotein apheresis: the ODYSSEY ESCAPE trial. *Eur Heart J*. 2016;37:3588–95.
13. Seidah NG. The PCSK9 revolution and the potential of PCSK9-based therapies to reduce LDL-cholesterol. *Glob Cardiol Sci Pract*. 2017;2017:e201702.
14. D'Erasmus L, Cefalu AB, Noto D, Giammanco A, Averna M, Pintus P, et al. Efficacy of lomitapide in the treatment of familial homozygous hypercholesterolemia: results of a real-world clinical experience in Italy. *Adv Ther*. 2017;34:1200–10.
15. Berberich AJ, Hegele RA. Lomitapide for the treatment of hypercholesterolemia. *Expert Opin Pharmacother*. 2017;18:1261–8.
16. Raal FJ, Hovingh GK, Blom D, Santos RD, Harada-Shiba M, Bruckert E, et al. Long-term treatment with evolocumab added to conventional drug therapy, with or without apheresis, in patients with homozygous familial hypercholesterolaemia: an interim subset analysis of the open-label TAUSIG study. *Lancet Diabetes Endocrinol*. 2017;5:280–90.
17. Thedrez A, Blom DJ, Ramin-Mangata S, et al. Homozygous familial hypercholesterolemia patients with identical mutations variably express the LDLR (low-density lipoprotein receptor): implications for the efficacy of evolocumab. *Arterioscler Thromb Vasc Biol*. 2018;38:592–8.
18. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
19. Morgan RL, Whaley P, Thayer KA, Schünemann HJ. Identifying the PECO: a framework for formulating good questions to explore the association of environmental and other exposures with health outcomes. *Environ Int*. 2018;121(1):1027–31.
20. Higgins JPT, Green S, editors. *Cochrane handbook for systematic reviews of interventions version 5.1.0* [updated March 2011] The Cochrane Collaboration. 2011. www.handbook.cochrane.org. Accessed 2 Dec 2024.
21. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol*. 2005;5:13.
22. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539–58.
23. Stein EA, Honarpour N, Wasserman SM, Xu F, Scott R, Raal FJ. Effect of the proprotein convertase subtilisin/kexin 9 monoclonal antibody, AMG 145, in homozygous familial hypercholesterolemia. *Circulation*. 2013;128:2113–20.
24. Raal FJ, Honarpour N, Blom DJ, Hovingh GK, Xu F, Scott R, et al. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2015;385:341–50.
25. Blom DJ, Harada-Shiba M, Rubba P, Gaudet D, Kastelein JJP, Charng MJ, et al. Efficacy and safety of alirocumab in adults with homozygous familial hypercholesterolemia: the ODYSSEY HoFH Trial. *J Am Coll Cardiol*. 2020;76:131–42.
26. Santos RD, Stein EA, Hovingh GK, Blom DJ, Soran H, Watts GF, et al. long-term evolocumab in patients with familial hypercholesterolemia. *J Am Coll Cardiol*. 2020;75(6):565–74.
27. Bruckert E, Caprio S, Wiegman A, Charng MJ, Zárate-Morales CA, Baccara-Dinet MT, et al. Efficacy and safety of alirocumab in children and adolescents with homozygous familial hypercholesterolemia: phase 3, multinational open-label study. *Arterioscler Thromb Vasc Biol*. 2022;42:1447–57.
28. Bansal S, Ruzza A, Sawhney J, Kulkarni G, Iyengar S, Mehta V, et al. Evolocumab in patients with homozygous familial hypercholesterolemia in India. *J Clin Lipidol*. 2021;15:814–21.
29. Banerjee P, Chan KC, Tarabocchia M, Benito-Vicente A, Alves AC, Uribe KB, et al. Functional analysis of LDLR (low-density lipoprotein receptor) variants in patient lymphocytes to assess the effect of evinacumab in homozygous familial hypercholesterolemia patients with a spectrum of LDLR activity. *Arterioscler Thromb Vasc Biol*. 2019;39:2248–60.
30. Raal FJ, Rosenson RS, Reeskamp LF, et al. The long-term efficacy and safety of evinacumab in patients with homozygous familial hypercholesterolemia. *JACC Adv*. 2023;2(9):100648.
31. Stefanutti C, Chan DC, Dip GZ, Watts GF. Real-world experience of long-term efficacy and safety of evinacumab in patients with homozygous familial hypercholesterolemia treated and not treating with lipoprotein apheresis. *J Clin Lipidol*. 2024;S1933–2874(24):00189–92.
32. Gaudet D, Greber-Platzer S, Reeskamp LF, Iannuzzo G, Rosenson RS, Saheb S, et al. Evinacumab in homozygous familial hypercholesterolaemia: long-term safety and efficacy. *Eur Heart J*. 2024;45:2422–34.
33. Béliard S, Saheb S, Litzler-Renault S, Vimont A, Valero R, Bruckert É, et al. Evinacumab and cardiovascular outcome in patients with homozygous familial hypercholesterolemia. *Arterioscler Thromb Vasc Biol*. 2024;44(6):1447–54.
34. Wiegman A, Greber-Platzer S, Ali S, Reijman MD, Brinton EA, Charng MJ, et al. Evinacumab for pediatric patients with homozygous familial hypercholesterolemia. *Circulation*. 2024;149:343–53.
35. Cholesterol Treatment Trialists (CTT) Collaboration, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010; 376:1670–1681.
36. Gu J, Gupta RN, Cheng HK, Xu Y, Raal FJ. Current treatments for the management of homozygous familial hypercholesterolaemia: a systematic review and commentary. *Eur J Prev Cardiol*. 2024;31:1833–49.
37. Musunuru K, Chadwick AC, O'Donnell CJ, et al. In vivo CRISPR base editing of PCSK9 durably lowers cholesterol in primates. *Nature*. 2021;593:429–34.
38. Moghadasian MH, McManus BM, Frohlich J, Hegele RA, Mancini GB, Hill JS, et al. Homozygous familial hypercholesterolemia: diagnosis, clinical manifestations, and management. *Am J Cardiovasc Drugs*. 2004;4:211–21.
39. Ruel I, Aljenedil S, Sadri I, Paquette M, Couture P, Genest J, et al. Aortic valve disease in homozygous familial hypercholesterolemia. *J Clin Lipidol*. 2016;10:105–12.
40. Stefanutti C, Blom DJ, Averna MR, Meagher EA, Theron HD, Marais AD, et al. The lipid-lowering effects of lomitapide are unaffected by adjunctive apheresis in patients with homozygous familial hypercholesterolaemia—a post-hoc analysis of a phase 3, single-arm, open-label trial. *Atherosclerosis*. 2015;240:408–14.
41. Rossi M, Fabris E, Barbisan D, Massa L, Sinagra G. Lipid-lowering drug therapy: critical approach for implementation in clinical practice. *Am J Cardiovasc Drugs*. 2022;22:141–55.
42. Santos RD, Ruzza A, Hovingh GK, et al. Evolocumab in pediatric heterozygous familial hypercholesterolemia. *N Engl J Med*. 2020;383:1317–27.
43. Alonso R, Diaz-Diaz JL, Arrieta F, et al. Clinical and molecular characteristics of homozygous familial hypercholesterolemia patients: insights from SAFEHEART registry. *J Clin Lipidol*. 2016;10:953–61.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.